REMARKS/ARGUMENTS

The present amendment is submitted in accordance with the *Revised Amendment Format* as set forth in the Notice provided on the USPTO web site for the Office of Patent Legal Administration; Pre-OG Notices; signed 1/31/03.

Claims 1-21 and 24-38 are pending in the application. Claims 24-38 are canceled without prejudice to subsequent revival. Applicants reserve the right to prosecute claims 24-38 in a divisional application. Claims 1-21 are examined on the merits. No claims are allowed.

Claims 1, 2, 4, 6, 9, 11, 14 and 19 have been amended. Claims 10, 20 and 22-23 have been canceled. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-9, 11-19 and 21 are requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was introduced by this amendment.

The specification has been amended to correct for an unintentional spelling error wherein the term "chimerics" has been replaced with the term "chimeras" in paragraph [026].

Claim 1 has been amended to replace the term "high" with "increased" for clarity and consistency. Support for this amendment can be found on page 6, paragraph [023], line 6. Claim 1 has further been amended to clarify that "the cell density" is maintained at "the increased cell density during step (d) as compared to the biomass grown to confluence during step (b)". Support for this amendment can be found on page 6, paragraph [023], lines 5-7. In addition, claim 1 has been amended to add the step "harvesting the virus or viral antigen produced" as suggested by the Examiner. Support for this amendment can be found on page 7, paragraph [028], lines 5-6.

Claim 2 has been amended to replace the term "concentrated" with "increased". Support for this amendment can be found on page 7, paragraph [027], lines 10-11.

Claims 4, 6, and 9 have been amended to include the term "consisting of" to provide for a proper Markush group. Claim 9 has also been amended to correct for an

unintentional spelling error, wherein the term "chimerics" was replaced with the term "chimeras". Support for this amendment can be found on page 6, paragraph [026], line 4.

Claims 11 and 14 have been amended to replace the term "high" with "increased" for clarity and consistency. Support for this amendment can be found on page 6, paragraph [023], line 6. Claims 11 and 14 have further been amended to clarify that "the cell culture" is maintained at "the increased cell density during step (d) as compared to the biomass grown to confluence during step (b)". Support for this amendment can be found on page 6, paragraph [023], lines 5-7. Claim 14 has also been amended to add a step of "harvesting the Influenza virus or Influenza virus antigen produced". Support for this amendment can be found on page page 7, paragraph [028], lines 5-6 and on page 11, paragraph [041], line 3.

Claim 19 has been amended to replace the term "concentrated" with "increased". Support for this amendment can be found on page 7, paragraph [027], lines 10-11.

Rejection Under 35 U.S.C. §112

Claims 1-21 have been rejected under 35 U.S.C. §112, second paragraph for being allegedly indefinite.

The office action indicates that claims 1, 11 and 14 recite "increased" cell density and "high" cell density. Herein, the Examiner requires clarification to what "increased" and "high" is measured against.

To the extent that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

Claims 1, 11 and 14 have been amended to replace the term "high" with "increased" for consistent reference to "the increased cell density". The term "increased" refers to an increased cell density when compared to the original biomass grown to confluence. The specification describes confluent cells to be between about 600,000 and 7,000,000 cells/ml (see page 6, paragraph [023], line 5). Furthermore, an increased cell density compared to the starting culture biomass is defined to be between at least about 800,000 and 9,000,000 cells/ml. From this it follows that the increase in density is at least 1.3 fold compared to the original biomass (see page 6, paragraph [023], line 3). Hence, the specification clearly defines what "an increased

cell density" is measured against, namely the original biomass grown to confluence. The claims have further been amended to clarify that the increased cell density during step (d) is compared to the biomass grown to confluence during step (b). As a result, the claims are definite.

Claims 1 and 14 are indicated to lack complete method steps. The claims have been amended to include the step of "harvesting" the virus or viral antigen as suggested by the Examiner.

Claims 4, 6, and 9 recite improper Markush groups as pointed out by the Examiner. The claims have been amended accordingly and now contain the term "consisting of".

In light of the amendment and the arguments presented above, Applicants respectfully request that the rejection of claims 1-9, 11-19 and 21 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. §102

Claims 1-5, 7, 8 and 10-13 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Giroux *et al.* (US Patent No. 5,994,134).

The rejection is respectfully traversed.

"In order for a rejection under §102(b) to be valid, each and every element of the claim must be found in the prior art reference." (MPEP 2131; *In re Royka and Martin,* 180 USPQ 580 (CCPA 1974)).

The instant invention is directed to a method of producing virus or viral antigen primarily for the purpose of efficient viral propagation and down stream vaccine production. As the Examiner correctly pointed out in the office action (page 3), the claims are drawn to a method of producing virus or viral antigen with cells bound to microcarriers, grown to confluence, infected with virus, incubated, harvested, and purified, wherein the cell density of the biomass of the cell culture is increased before or after infection. As stated in the specification (see page 4, paragraph [016]), the Applicants surprisingly found that *reduction of the culture medium* volume prior to or after infection with the virus (*wherein the cell density* and microcarrier concentration in the cell culture biomass are *increased*) does not influence the

productivity of the cells. Even more surprising was the fact that the ultimate virus yield per cell is increased compared to the virus yield of cells that are maintained at the same cell density as the original confluent cell culture. This was unexpected because a higher cell density normally leads to higher physiological stress (*e.g.*, cells slough off the microcarriers) and to a reduction of cell viability and less virus yield. The fact that the claimed method leads to the production of increased virus yield is not only surprising but also entirely novel. The method is further illustrated by the Examples (see pages 11-16), wherein it is shown that the cell culture grown to confluency was concentrated by sedimentation of the biomass to reach a two-fold concentration (see page 13, paragraph [048]) resulting in a total antigen concentration of 412.3 (495%) compared to 83.3 (100%) at confluent cell culture conditions (see TABLE 2, page 14).

In comparison, Giroux (Giroux *et al.*) teaches a method of producing *recombinant advenoviral vectors* at high titers in a cell culture system using 293 cells, primarily for production of recombinant replication defective adenoviruses containing an exogenous transgene (see column 1, lines 49-52). Moreover, Giroux does not teach a method wherein the cell density of the biomass of the cell culture is increased before or after infection. As a result, Giroux does not teach step (d) of the claimed method. Notably, the Examiner points to a specific passage, *i.e.*, column 12, lines 1-3 of the reference, wherein Giroux teaches that an increased virus concentration at the infection phase enhances the production of virus in the producer cell. However, an *increased virus concentration per cell* does not equal an increase in cell density. As Giroux elaborates further in column 12, one should strive to maintain the infections in the virus concentration in the range of 10^6 to 10^{10}, preferably 10^9 virions per ml. Thus, Giroux is referring to an increase in infectious units per cell and not an increase in cell density. This is further explained in column 14, lines 29-32, wherein Giroux discloses that cells were cultured until the cell density reached the desired level (8-10 x 10^6 cells/ml or approximately 230 cells per microcarrier). The reference then goes on to describe that 5 x 10^{12} particles of adenovirus were added to the culture vessel to infect the cells (see column 15, lines 6-10). It is clear from the reference disclosure that Giroux does not increase the cell density of the cell culture before or after infection with the virus. Hence, Giroux does not anticipate the claimed invention.

In light of the arguments presented above, Applicants respectfully request that the rejection of claims 1-5, 7, 8 and 10-13 under 35 U.S.C. §102(b), be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 6, 9 and 14-21 are rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Giroux *et al.* (US Patent No. 5,994,134) as applied to claims 1-5, 7, 8 and 10-13 above, and further in view of Webster *et al.* (US Patent No. 6,344,354) and Gröner *et al.* (US Patent No. 6,455,298).

The office action indicates that Webster teaches the production of Influenza virus in VERO cells and MDCK cells, and that it would have been obvious to produce Influenza virus in Giroux's method because Webster allegedly established that there is a long-felt need in the art for a method of Influenza virus and vaccine production. The Examiner also asserts that one would have had a reasonable expectation of success that Influenza virus would have been produced in Giroux's method because Gröner teaches the production of Influenza virus using cells growing adherently on microcarriers.

The rejection is respectfully traversed.

As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As shown above, Giroux does not anticipate the instant invention because Giroux does not increase the cell density of the cell culture before or after infection with the virus. Thus, Giroux's disclosure coupled with the knowledge that influenza virus can be produced in VERO cells and MDCK cells (see Webster) and/or the knowledge that the production of influenza virus may be accomplished by using cells that grow adherently on microcarriers (see Gröner) does not teach or suggest to the skilled artisan to produce the claimed invention. There is simply no motivation to combine the references because applying Giroux's method to Webster and/or Gröner would not lead to the claimed method.

As the Examiner is further aware, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). However, in this case the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

As discussed above, Giroux does not teach increasing the cell density of the cell culture before or after infection with the virus. The other two references cited by the Examiner do not discuss this limitation either. In fact, the Examiner has pointed to nothing in the secondary references that teaches or suggests this element of the claimed method. Since in each case, all of the claim limitations are not suggested by the combination of references, the rejection should be withdrawn.

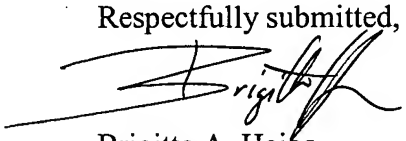
In light of the arguments presented above, Applicants respectfully request that the rejection of claims 6, 9, 14-19 ands 21 under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Brigitte A. Hajós
Reg. No. 50,971

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
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